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Biological Responses Differ Considerably Between Endovascular and Conventional Aortic Aneurysm Surgery*

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Objectives: *To determine the inflammatory responses in endovascular abdominal aortic aneurysm (AAA) repair and their relation to clinical findings.*
Design: *Prospective non-randomised study.*
Setting: *University Hospital, Department of Surgery.*
Patients and methods: *Seven patients treated with an endoluminal procedure (AAA-E) and seven patients undergoing conventional surgery (AAA-C) were included. Inflammatory parameters were assessed by measurements of the cytokines interleukin (IL)-1β, IL-6, IL-8 and Tumour Necrosis Factor-alpha (TNF-α); analyses of complement proteins C1q, C4, C3, C5a and Terminal Complement Compexes (TCC);* haematologic parameters *and determination of C-reactive protein (CRP).*
Results: *In six of seven patients in the AAA-E group blood pressure decreases were recorded during introduction of the device. IL-6 and CRP levels were found to be significantly higher in AAA-C patients compared to the AAA-E group. On the other hand, high TNF-α levels were recorded in the AAA-E group. Less consumption of the complement proteins C1q, C4 and C3 was observed in AAA-E compared to AAA-C patients. Increased C5a levels were recorded in the AAA-C group, whereas only slight fluctuations were noticed in the AAA-E group. TCC levels were unchanged in both groups.*
Conclusion: *Endovascular aortic aneurysm repair induced a significant inflammatory response, mainly involving TNF-α and differing from the findings during open AAA repair. These inflammatory responses were probably related to blood pressure decreases during the procedures. On the other hand, conventional repair induced responses related to the more extensive surgical trauma and reperfusion injury.*

Key Words: Endovascular; Aortic aneurysm; Cytokines; Complement.

Introduction

Conventional surgery for abdominal aortic aneurysm (AAA) is an accepted procedure, however, the operation is extensive and with considerable morbidity. An endovascular technique allowing repair without laparotomy and aortic clamping has the potential to reduce this morbidity. Early experiences from endoluminal placement of stent-supported grafts to treat abdominal aortic aneurysms are encouraging.[1–5] Elective aortic surgery, utilising synthetic graft-material and studies of vascular graft materials *in vitro* have shown systemic reactions and inflammatory responses.[6–11] Although some reports have been presented on clinical side effects[12–14] so far nothing has been published on cellular responses to the endovascular procedures. During our first endovascular procedures we found intraoperative decreases in blood pressure and closely related TNF-α increases.

The aim of the present study was therefore to determine the inflammatory response during and after endovascular grafting of aortic aneurysms in relation to the clinical findings.

Materials and Methods

Seven patients with a vascular morphology eligible for an endoluminal procedure (AAA-E) and seven patients undergoing conventional aortic aneurysm surgery (AAA-C) during the same time period were

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Table 1. Characteristics of patients treated for abdominal aortic aneurysm by endoluminal technique (AAA-E) or conventional surgery (AAA-C)

	AAA-E	AAA-C
Age (years) (median and range)	63 (52–72)	74 (69–80)
Sex		
Male	7	7
Female	—	—
Clinical history		
Hypertension	2	5
Myocardial infarction	3	2
Diabetes mellitus	—	—
Chronic pulmonary disease	2	2
Cerebrovascular disease	—	2
Smoking habits		
Smoker	5	5
Non-smoker	2	2

included, all were male patients, 52–80 years of age. Demographic data are presented in Table 1.

Surgical technique

Both endovascular AAA repair and conventional aortic aneurysm surgery were performed under general anaesthesia with the addition of an epidural block. In the endovascular group bilateral preparation of the femoral artery was performed in all but one case. Technically all seven procedures in the AAA-E group were successful, ending up with six aortobiiliac grafts and one aortic tube graft (Stentor® and Endopro® systems, MinTec, La Ciotat, France). In the AAA-C group four aortobiiliac bypass procedures were performed and three patients received a tube graft (Woven Dacron, ULP®, Intervascular, La Ciotat, France).

All patients in the AAA-E group and two patients in the AAA-C group received 5000 IU heparin intravenously before balloon inflation and clamping, respectively. Pre-, per- and postoperative clinical signs including body-temperature, operation and clamping time, blood loss, blood transfusion and other infusions were recorded. Approval from the Ethics Committee of Lund University and informed consent from the patients were obtained.

Venous blood was collected in pyrogen-free tubes with and without ethylene diamine tetra-acetic acid (EDTA). Samples were collected one day prior to surgery; after induction of anaesthesia; immediately before balloon inflation or aortic clamping ("pre-clamp"); immediately after balloon deflation or declamping ("post-clamp"); 60 min; 6, 24, 48 h; 3 and 7 days after balloon deflation or declamping ("post-clamp"). Samples were immediately centrifuged at 3000 rpm for 10 min. Separated plasma and serum were directly stored in aliquots at –80°C. A complete blood-cell count including haemoglobin, platelets and differential count was performed at each time-interval.

Laboratory technique

IL-1β, IL-6 and TNF-α in plasma were measured using an ELISA (Immunotech S.A., Marseille, France; Medgenix Diagnostics, High Wycombe, U.K. and Innogenetics Inc., Antwerp, Belgium respectively). IL-8 in plasma was measured by ELISA. Briefly, 96-well microtiterplates (Nuclon A/S, Roskilde, Denmark) were incubated overnight with a monoclonal antibody to IL-8 (1.2 μg/ml). After washes, standards and samples were incubated for 2 h at 37°C. Then an alkaline phosphate conjugated polyclonal goat IL-8 antibody was added and the plates incubated for 2 h at 37°C. Thereafter p-nitro-phenyl phosphate was added and incubated for 30 min in the dark. The plate was read in a multiscan spectrophotometer at 405 nm.

Serum C1q, C4 and C3 were measured with an electroimmunoassay.[15–17] Serum C5a was measured using a commercially available radioimmunoassay (Amersham, Buckinghamshire, U.K.). Soluble terminal complement complexes (TCC) (SC5b-C9) were quantified in plasma with an ELISA using a monoclonal antibody specific for a neoepitope of activated C9[18] (gift from Dr. E Mollnes, Tromsø, Norway). Zymosan-activated serum was used as a standard, stated to contain 10.000 Arbitrary Units (AU)/ml. Haemoglobin (Hb)-concentration was used for correction of the hemodilution effects on concentrations of complement proteins, which were multiplied by the factor: preoperative Hb/postoperative Hb.

Comparisons between the AAA-E and AAA-C groups were made with a non-parametric analysis (Mann-Whitney U-test). Data are presented as mean (± S.E.M.).

Results

Clinical findings

Surgical data are presented in Table 2. The aneurysm diameter was significantly larger in patients who underwent conventional aneurysm repair ($p < 0.05$).

Both blood loss and fluid infusions were significantly higher in the AAA-C group ($p < 0.0005$ and $p < 0.005$ respectively) compared to the AAA-E group. Blood transfusion was given in three out of seven patients in the AAA-C group. The endovascular procedures were as time consuming as the open ones. The insertion of the endovascular introducer into the aorta and maneuvers unrelated to any balloon occlusion of the vessel caused a sudden blood pressure drop from a mean of 109 mmHg down to 68 mmHg in six out of seven patients in the AAA-E group (range 90–130 to 58–79 mmHg). In the majority, peripheral vasodilation was noted. The body-temperature was significantly higher in the AAA-C group between six and 24 h postoperatively, whereas 2–5 days postoperatively significantly higher temperatures were recorded in the AAA-E group (Fig. 1).

Table 2. Surgical data of patients treated for abdominal aortic aneurysm by endoluminal technique (AAA-E) or conventional surgery (AAA-C)

	AAA-E Mean (S.E.M.)	AAA-C Mean (S.E.M.)
Aneurysm diameter (mm)	46 (3.2)	62 (6)*
Duration surgery (min)	198 (32)	218 (13)
Cross clamping aorta (min)	—	67 (6)***
Blood loss (ml)	200 (54)	1983 (478)***
Infusion volume (ml)	2521 (449)	5386 (665)**
Blood administered (ml)	—	357 (203)

*$p<0.05$, **$p<0.005$ and ***$p<0.0005$.

In the AAA-E group one patient developed a condition resembling a septic shock syndrome the first postoperative day but recovered within 24 h. Twenty-four hours after surgery this patient also reported a sudden pain in the thighs and some weakness in the legs. Examination suggested an ischaemic neuropathy at the lumbosacral plexus level. The symptoms gradually disappeared and good recovery was seen after 1 week. Another patient in this group developed acute ischaemia of the left leg 14 days postoperatively. Angiography showed a graft-occlusion at the iliac level and a partial occlusion also on the right side. During exploration it was decided to remove the device, which was surgically replaced by a bifurcated Dacron graft. The other five patients had an uneventful postoperative course. One of them, however, had a slowly diminishing leakage.

In the AAA-C group one patient who was discharged after 7 days without postoperative complications died 28 days later due to myocardial infarction. One patient developed signs of bowel obstruction on the third postoperative day. Laparotomy revealed a paralytic ileus without signs of bowel ischaemia or obstruction.

Laboratory findings

Leukocytes and monocytes decreased significantly

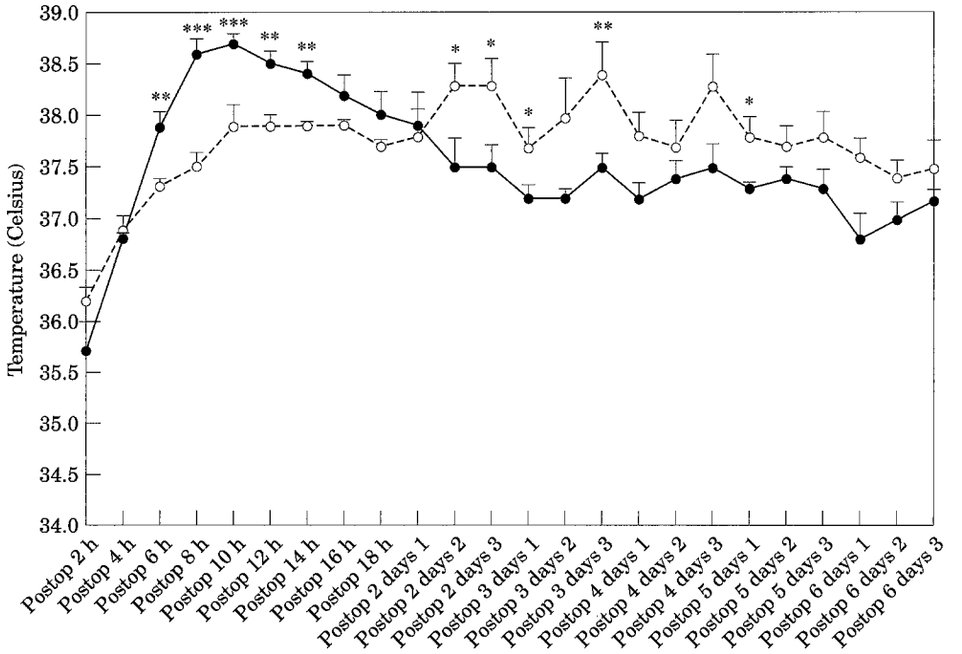

Fig. 1. Body-temperature postoperatively (non-linear time-scale). Data are presented as mean ± S.E.M.* $p < 0.05$, ** $p < 0.005$ and *** $p < 0.0005$. (●) AAA-C; (○) AAA-E.

($p < 0.0005$) 60 min "post-clamp" in the AAA-E group compared to the AAA-C group (Figs. 2a and b). Moreover, monocytes could not be detected in the blood samples in four out of seven AAA-E patients at this time-point. Platelets decreased and followed in all patients the same pattern (Fig. 2c).

Circulating TNF-α was only detected in patients who underwent an endovascular procedure. The AAA-E patient with no TNF-α did not show a blood pressure drop. The highest TNF-α values were observed 60 min "post-clamp" (Fig. 3). Within 48 h, TNF-α levels were no longer detected.

Il-1β demonstrated a maximum at 60 min "post-clamp". Values declined thereafter to zero. No difference was found between the two groups. The IL-6 response increased "post-clamp". A low response was seen in the AAA-C group (Fig. 4a). A maximum was reached in this group at 24 h with a subsequent rapid return within 1 day. Preoperative IL-6 levels were reached within seven days in both groups. IL-8 was not detected in any patient.

CRP-concentrations peaked 2 and 3 days after conventional aortic aneurysm repair and endovascular procedures respectively. CRP was significantly lower ($p < 0.05$) at 48 h and decreased more rapidly after 3 days postoperatively in the AAA-E group compared to the AAA-C group (Fig. 4b). Concentrations of complement proteins C1q, C4 and C3, corrected for hemodilution, decreased all during and/or after surgery. In the AAA-E group a significantly lower decrease of C1q was observed between "pre-clamp" and three days postoperatively compared to

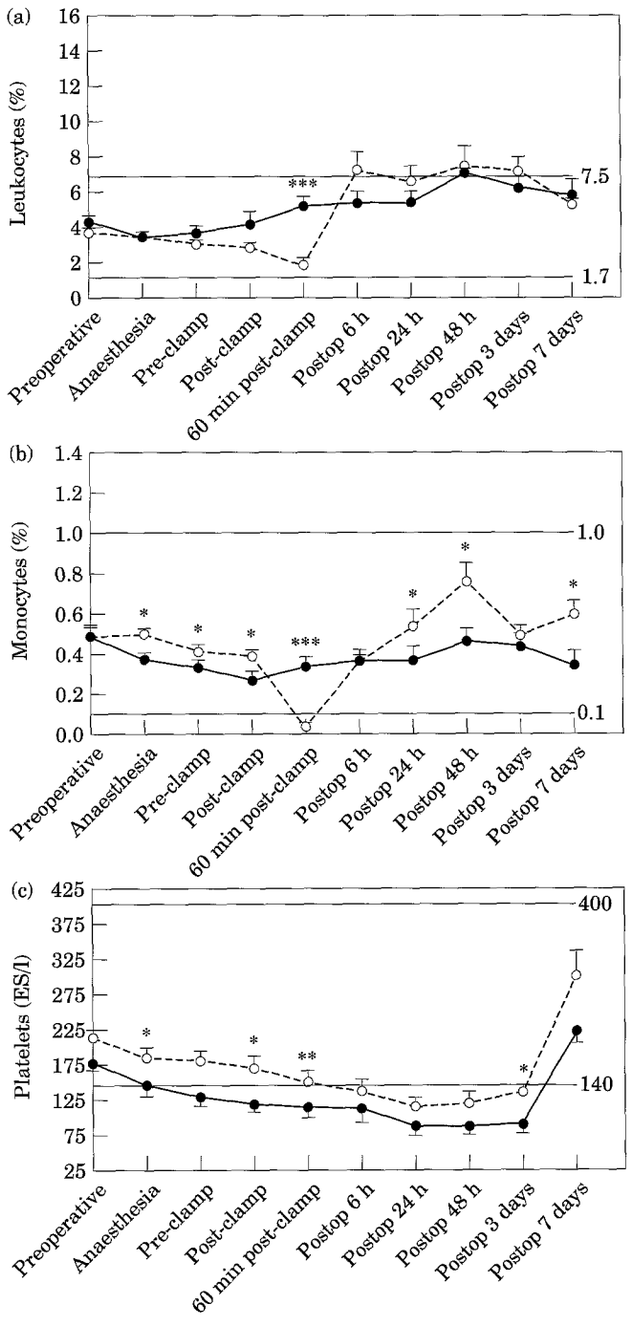

Fig. 2. Percentage leukocytes (a), monocytes (b) and platelet count (c) preoperatively, during surgery and postoperatively (non-linear time-scale). Baselines indicate minimum and maximum normal values. "Pre-clamp" means immediately before balloon inflation or aortic clamping; "Post-clamp" means immediately after balloon deflation or declamping. Data are presented as mean ± S.E.M.* $p < 0.05$, ** $p < 0.005$ and *** $p < 0.0005$. (●) AAA-C; (○) AAA-E.

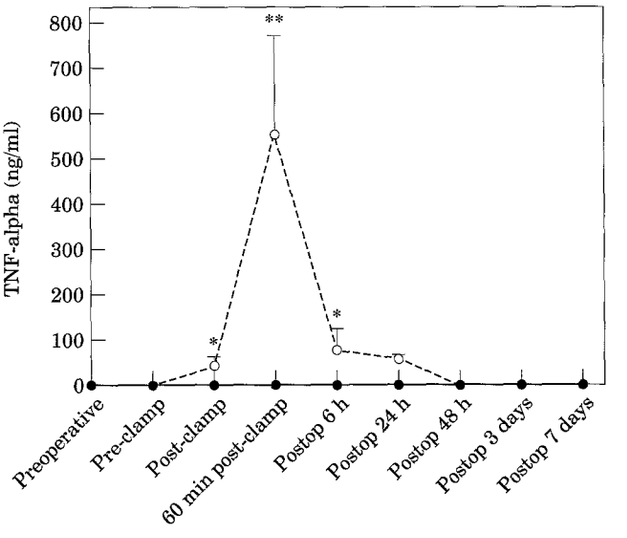

Fig. 3. Time course of TNF-α release in patients undergoing endovascular aortic aneurysm repair (non-linear time-scale). No systemically detected TNF-α levels were found in the AAA-C group. "Pre-clamp" means immediately before balloon inflation or aortic clamping; "Post-clamp" means immediately after balloon deflation or declamping. Data are presented as mean ± S.E.M. * $p < 0.05$ and ** $p < 0.005$. (●) AAA-C; (○) AAA-E.

the AAA-C group. The most pronounced decrease was noticed 24 h after surgery in both groups, normalised at day 7 (Fig. 5a). The C4 levels remained unchanged during the endovascular procedure followed by a slight decrease between 6 and 48 h postoperatively (Fig. 5b). Thereafter the C4 protein level increased above preoperative values at the seventh postoperative day. In the AAA-C group a decrease was observed immediately after induction of anaesthesia. The maximum decline was recorded 6 h after surgery (Fig. 5b). The difference between the two groups was significant during "post-clamp" to 3 days postoperatively. C3 proteins followed the same pattern as C4 proteins with significant differences observed between 60 min "post-clamp" and 6 h postoperatively ($p < 0.05$). A significant increase of the anaphylatoxin C5a (Fig. 5c) was observed in the AAA-C group from 24 to 48 h after surgery. The highest values were reached 3 days postoperatively and C5a normalised within 7 days. No significant change in C5a concentra-

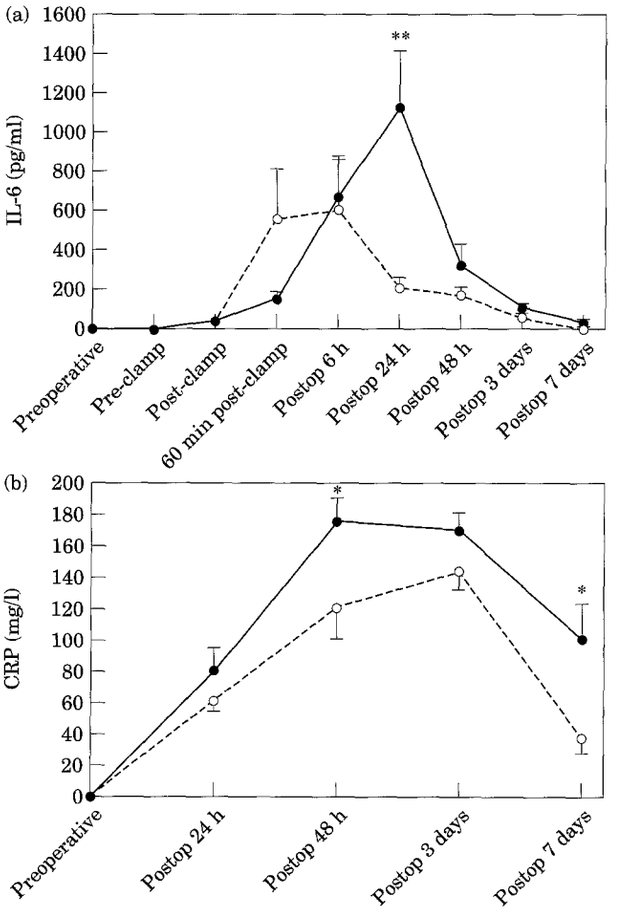

Fig. 4. Time course (non-linear time-scale) of IL-6 (a) and C-reactive protein (CRP) (b). "Pre-clamp" means immediately before balloon inflation or aortic clamping; "Post-clamp" means immediately after balloon deflation or declamping. Data are presented as mean ± S.E.M. * $p < 0.05$ and *** $p < 0.0005$. (●) AAA-C; (○) AAA-E.

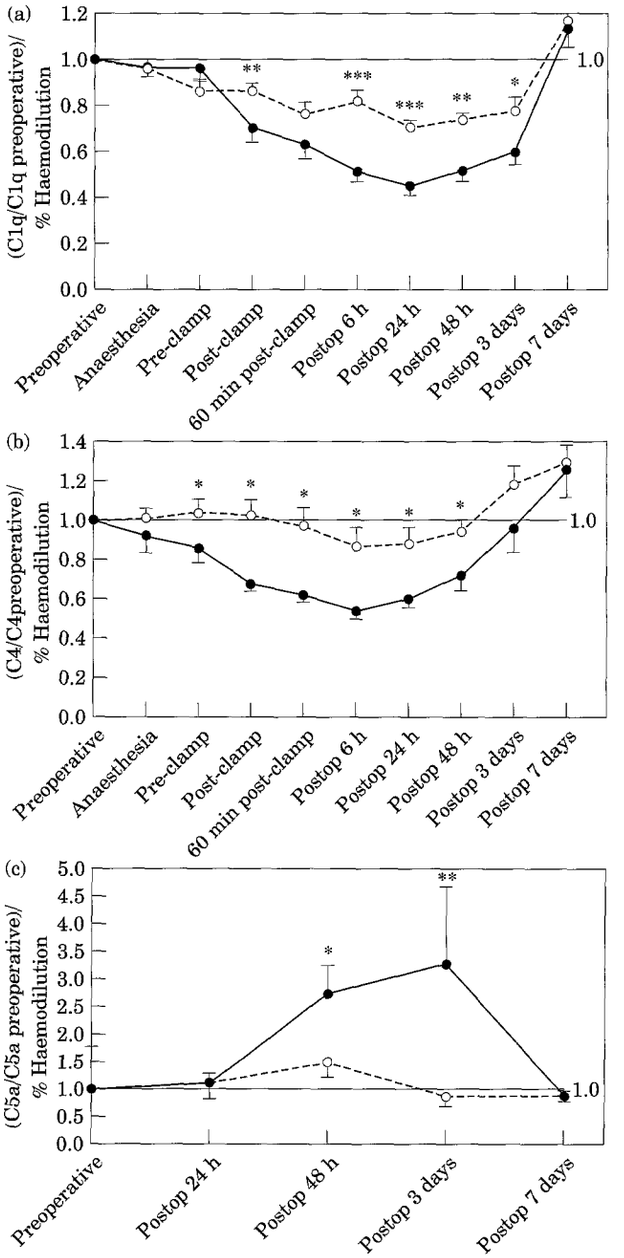

Fig. 5. Time course (non-linear time-scale) of C1q (a), C4 (b) and C5a (c) concentration pre-, intra- and postoperatively expressed as C1q/C1q preoperatively; C4/C4 preoperatively and C5a/C5a preoperatively respectively. "Pre-clamp" means immediately before balloon inflation or aortic clamping; "Post-clamp" means immediately after balloon deflation or declamping. Data are presented as mean ± S.E.M. and are corrected for haemodilution. * $p < 0.05$, ** $p < 0.005$ and *** $p < 0.0005$. (●) AAA-C; (○) AAA-E.

tion was demonstrated in the AAA-E group. TCC levels were unchanged in both groups.

Discussion

Considerable inflammatory response and signs of complement activation are known to occur during open aortic surgery.[6–10] The present study demonstrated that endovascular aortic aneurysm repair in six out of seven patients caused a transient biochemical response resembling a septic reaction or a systemic inflammatory response syndrome (SIRS) with TNF-α release, while the surgical trauma response (IL-6) was limited, contrary to the findings during conventional aortic aneurysm surgery. The same patients also had a blood pressure decline during insertion of the endovascular device. Only one patient, however, had a clinical SIRS postoperatively. One major difference between endovascular and conventional aneurysm surgery is that the thrombotic content of the aneurysm is left intact during endovascular procedures. Bacterial growth has been reported from this thrombotic content, most commonly *S. epidermidis*.[19] Manipulation into the aneurysmal thrombotic content with a large introducer may imply microembolisation but also cellular activation and thereby cytokine release, mimicking a septic or SIRS reaction. Clinical signs of microembolisation were not seen, except that the patient with SIRS also experienced symptoms which might have been related to microembolisation of the lumbosacral plexus.

TNF-α and IL-1β play a critical role in mediating SIRS.[20] Experimental endotoxaemia achieved by injection of E. coli bacteria in humans, has induced fever, cytokinaemia and several haematological and endocrinological effects which are characteristic of infection and inflammation.[21,22] Elevated levels of TNF-α and IL-1β have been recorded.[22,23] In the present study only TNF-α release was demonstrated in the AAA-E group, whereas the IL-1β response was equal in both groups. However, IL-1β response is known to follow after the TNF-α response and therefore maximum values of IL-1β could have been overseen, since no blood samples were taken between 60 min and 6 h "post-clamp".

TNF-α release may induce hypotension. It could well be that such a release explains the blood pressure decreases which were recorded in most patients during the endovascular procedure, since the single AAA-E patient with a stable blood pressure during the procedure had no systemic TNF-α release. It should also be noted that no active lowering of the blood pressure was induced at insertion of the device. Both TNF-α and IL-1β may induce fever as well. However, the significantly higher temperatures in the AAA-E group compared to the AAA-C group were demonstrated when no longer TNF-α or IL-1β were detected in the blood samples. It could be argued that local inflammation, without systemic cytokine increase, is sufficient to cause increased body temperature. Another possibility is that fever is induced by other, so far undefined causes.

The question may also arise whether a true septic reaction due to bacteraemia could occur. We connot answer that question as only sporadic samples for cultures were taken. No bacterial growth was, however, recorded. The fact that an anaerobic growth is found in a considerable number of aneurysms[19] leaves the question open.

The almost total absence of monocytes and the significant decrease of leukocytes 60 min "post-clamp" in the AAA-E group might be explained by a massive adherence to the graft-supported stent or by a massive shift of these cells to inflammatory sites. However, the white blood cells were restored within six hours and the clinical importance of this phenomenon is so far unknown.

The IL-6 response may reflect tissue damage due to ischaemia and reperfusion or the surgical trauma *per se*.[6] The limited IL-6 response recorded in the AAA-E group is consistent with this hypothesis. Moreover, IL-6 is known to correlate with the development of postoperative inflammatory complications.[6] The IL-6 levels of the four patients with major complications (two patients in each group) were significantly higher and persisted longer than the response seen in patients with an uneventful postoperative course. IL-6 constitutes furthermore a major regulator of the acute phase response in human hepatocytes.[24,25] IL-6 responses peaked between 6–24 h and CRP between 48–72 h, which is consistent with findings in other studies.[6,26,27] Decreased concentrations of native complement proteins C1q, C4 and C3 was demonstrated, which usually reflects consumption due to complement activation. The decrease of these proteins was significantly less pronounced in the AAA-E group. Consistent with complement activation the concentration of anaphylatoxin C5a increased significantly after open aortic surgery, whereas only slight fluctuations of C5a were seen in the AAA-E group. Complement activation may therefore be related to the magnitude of the surgical trauma. TCC formation might be concomitant with C5a release, however, no elevated TCC levels were found in the present study. Due to a lower sensitivity of the TCC-ELISA compared to the

C5a RIA-assay, elevated TCC levels might not have been detected.

The study did not intend to randomise patients to the two treatment groups. All patients with a morphology suitable for an endovascular procedure were treated that way. There was therefore a selection of larger aneurysms to the AAA-C group. There was no difference regarding inflammatory parameters preoperatively between the groups. The greater inflammatory response in the AAA-E group is unlikely to be related to the fact that this group included the smaller aneurysms. Larger fluid volumes were infused in the conventional group compared to the endovascular group. If IL-6 and CRP had been corrected for haemodilution, higher levels would have been demonstrated which would have enhanced the observed differences. Complement proteins, which are known to be influenced by haemodilution were already corrected for this phenomenon. Heparin was given routinely to all AAA-E patients but only in two AAA-C cases. The main reason for this prophylaxis is to avoid thrombotic and embolic complications. It is unlikely that the presented results in any way were influenced by this difference between the groups.

In conclusion, endovascular aortic aneurysm repair induced a significant inflammatory response with TNF-α release which differed from the response during open AAA repair and the response was related to the clinical finding of blood pressure decrease during the procedures. Conventional AAA repair induced responses in line with the more extensive surgical trauma. Further studies on the inflammatory and immunologic responses occuring during endovascular surgery may help to explain these unexpected reactions, which have to be more clearly defined to enable possible prevention. Whether technical modifications should be advised, in order to minimise the manipulation inside the aortic aneurysm, is open to question.

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